



General recommendations paper on the management of older patients with cancer: the SEOM geriatric oncology task force's position statement

R. Gironés Sarrió¹ · M. Antonio Rebollo² · M. J. Molina Garrido³ · C. Guillén-Ponce⁴ · R. Blanco⁵ · E. Gonzalez Flores⁶ · J. Saldaña² · On behalf of the Spanish Working Group on Geriatric Oncology of the Spanish Society of Medical Oncology (SEOM)

Received: 18 February 2018 / Accepted: 2 March 2018
© The Author(s) 2018

Abstract

Population aging is associated with greater numbers of older people with cancer. Thanks to treatment advances, not only are more seniors diagnosed with cancer, but there are also more and more older cancer survivors. This upward trend will continue. Given the heterogeneity of aging, managing older patients with cancer poses a significant challenge for Medical Oncology. In Spain, a Geriatric Oncology Task Force has been set up within the framework of the Spanish Society for Medical Oncology (SEOM). With the aim of generating evidence and raising awareness, as well as helping medical oncologists in their training with respect to seniors with cancer, we have put together a series of basic management recommendations for this population. Many of the patients who are assessed in routine clinical practice in Oncology are older. CGA is the basic tool by means of which to evaluate older people with cancer and to understand their needs. Training and the correct use of recommendations regarding treatment for comorbidities and geriatric syndromes, support care, and drug–drug interactions and toxicities, including those of antineoplastic agents, as detailed in this article, will ensure that this population is properly managed.

Keywords Geriatric oncology · Spanish society for medical oncology · Geriatric oncology task force · Aging

Introduction

The gradual aging of the world's population, the greater risk of developing neoplasms at older ages, and the lack of scientific evidence have made the management of older individuals with cancer a tremendous care challenge [1]. Though significant strides have been made in recent years in awareness raising and research into aging and cancer, the

care experience in Spain is limited to individual initiatives, with no national structure in place to approach this population cohort [2].

Aging is a highly disparate process, and as such, and given that chronological age does not always correspond with biological age, a patient's date of birth should not be used as the sole discriminatory element when embarking on a diagnostic process or establishing the best treatment option for a specific neoplastic disease. One of the main difficulties lies in the very definition or diagnosis of aging. Despite the growing body of research in this field, thus far, we have no useful biological markers for care practices that enable us to determine a person's biological age and aid us in treatment decision-making. At present, the only valid tool we have to ascertain the true biological status of an older individual with cancer is a comprehensive geriatric assessment (CGA) [3, 4]. While CGA is a widely used tool in various medical specialties, there is no consensus as to the scales to be used; furthermore, it calls for an investment of time and expertise that we are hard-pressed to assume within the reality of our

✉ R. Gironés Sarrió
reginagiro@hotmail.com

¹ Medical Oncology Unit, Hospital Lluís Alcanyís, Crta Xàtiva A Silla Km 2, Xàtiva, 46800 Valencia, Spain

² Institut Català d'Oncologia, Barcelona, Spain

³ Hospital General Virgen de la Luz, Cuenca, Spain

⁴ Hospital Universitario Ramón and Cajal, Madrid, Spain

⁵ Consorci Sanitari de Terrassa, Barcelona, Spain

⁶ Hospital Virgen de las Nieves, Granada, Spain

care systems. There have been numerous proposals for simplified circuits or alternate variants in recent years, yet no consensus has been reached regarding a common strategy that would enable trials to be conducted to obtain scientific evidence and establish treatment protocols for each disease scenario [5].

In 2015, the Spanish Geriatric Oncology Group was created within the Spanish Society for Medical Oncology (SEOM) with the intention of analyzing the situation of geriatric oncology in Spain and to raise the awareness of professionals and political decision makers about the need to have a structured approach to this growing population. The main aim of the group is to approach geriatric oncology from an imminently pragmatic perspective; i.e., to provide the oncologist with a shared lexicon and simple, agreed upon tools that will be useful in real-world routine care and enable research to be conducted that focuses on responding to those situations in which we currently have no scientific evidence [2].

This document has been drafted with the purpose of providing general recommendations as to the evaluation and therapeutic management of the older patient with cancer. To this end, the first section has reviewed the concept of Geriatric Assessment, as well as the different scales that comprise it, focusing the second section on general recommendations to optimize management of seniors with cancer, regardless of the specific disease to be treated.

Recommendations regarding evaluation and scales

Older individuals have less physiological reserve [6, 7] and, therefore, present a higher risk for iatrogenic complications [8]. They frequently suffer multiple diseases and geriatric syndromes, have a broad history of medications, and are often socially and functionally vulnerable. All this points to the fact that they require a comprehensive appraisal of their health status, including medical, cognitive, psychological, social, and functional aspects of daily life. Comprehensive Geriatric Assessment (CGA) systematically covers these key areas from a multidisciplinary perspective [9, 10] and to do so, must use valid, reliable, and sensitive measurement tools. It will thereby be capable of evaluating the changes individuals undergo over time against their baseline status. In this way, CGA will inform us as to the true situation of the person we are caring for, not only with respect to their age, but to their situation of biological vulnerability (whether they are robust or vigorous, pre-frail, frail, or dependent).

The scientific evidence available indicates that CGA in seniors with cancer provides more information than would otherwise be the case with only the physician's intuition, making it an essential tool in Geriatric Oncology [11, 12].

Data from CGA lead to a modification of the treatment plan initially proposed by the specialist, and, therefore, supplies more information than the traditional assessment performed in younger patients [13–16]. The guidelines of the National Comprehensive Cancer Network (NCCN) recommend conducting CGA in individuals with cancer ≥ 65 years of age [17]. SIOG advises that all seniors seeking care undergo CGA [16], particularly in those with a treatment indication for their neoplasm.

The definition of who should undergo CGA will ultimately depend, too, on the availability of resources and on how care is organized at each center.

The transcendence of CGA in Geriatric Oncology links the advantages of CGA in older people with any disease with other specific advantages in seniors with cancer [18]: estimation of life expectancy [19–21], the risk of chemotherapy-derived toxicity [19, 22, 23] and early treatment suspension, or the possibility of functional decline [24, 25].

Insofar as the domains, a CGA should appraise is concerned, and SIOG drafted a consensus document in 2005, the latest update of which was published in 2014 [16]. In their consensus, they established that the domains that should appear in any CGA model are functional status, comorbidity, cognitive status, emotional state, social situation, nutritional status, and the presence of fatigue and geriatric syndromes [16]. Despite these recommendations, a recent publication-addressing seniors undergoing chemotherapy reflected that certain components of CGA are only ascertained in a small percentage of older patients [26].

As regards the scales to be used to appraise each domain, in SIOG's latest consensus, no model was deemed superior to another [16]. Two consensus statements were drafted to determine the domains and scales to be used. One was carried out in United States [27] and the other was conducted at the international level [28]; in both cases, consensus was reached. In Spain, a consensus was also attained by SEOM's task force on Geriatric Oncology. There is a Spanish consensus derived from the SEOM Geriatric Oncology Expert Committee with respect to the domains to be appraised by CGA and the scales to be used. The main conclusions regarding the domains and scales to be used in evaluating seniors with cancer are presented in Table 1 [2].

General treatment management recommendations for seniors with cancer

Once the patient has been assessed as we have previous described and based on the circuits and resources available at each center, an individualized treatment proposal will be made.

Whatever the proposal is, there is a series of general considerations to be taken into account in treating any older

Table 1 Domains and scales recommended by the SEOM's Geriatric Oncology Expert Committee

Domain	Scale
Functional	
ADL	Barthel scale
AIVD	Lawton–Brody Index
Functional status	Gait speed
Nutritional	MNA
Cognitive	Pfeiffer Questionnaire
Mood	Yesavage Questionnaire
Socio-familiar	Gijón social-familiar scale
Comorbidity	Charlson Index
Drug use	Number of medications
Geriatric syndromes	Insomnia
	Visual and auditory acuity
	Fecal and urinary incontinence
	Pressure sores
	Abuse

MNA mini-nutritional assessment, *ADL* activities of daily living, *IADL* instrumental activities of daily living

patient with cancer. First of all, the individual's comorbidities must be ascertained as well as how to intervene specifically with respect to the geriatric syndromes detected in the CGA. We must choose chemotherapy schedules or other cancer-specific treatments with the lowest toxicity and any treatment-induced effects must be prevented and aggressively treated as early as possible when, despite our best efforts, they do arise. Likewise, proper functional monitoring must be performed, depending on the person's comorbidities and the guidelines used. Finally, adequate symptomatic control is imperative.

Treatment and comorbidity stabilization

The presence of comorbidities can affect the treatment of cancer in seniors in very different ways [29]: comorbidities can influence how cancer behaves [30] and can hasten or delay its diagnosis; cancer treatment can worsen the comorbidity or entail unacceptable risk; the presence of comorbidities can condition life expectancy [31], and, finally, comorbidities can affect the results of oncological treatment [32].

Specific intervention on the geriatric syndromes detected

As previously described, geriatric syndromes can be detected by CGA, evaluating the different biomedical and psychosocial domains as per protocol. Thus, we can often encounter a subacute functional decline that can sometimes improve through a multidisciplinary intervention. Discovering a

situation of risk for falls will also enable us to implement preventive measures [33] and train the caregiver. The risk of suffering pressure sores due to immobilization is also not at all unusual and detecting it will also allow preventive measures to be put into place and an efficacious approach to be taken. The nutritional assessment incorporated into our appraisal can reveal patients who are at risk for malnutrition [34, 35], as well as those who can already be diagnosed as being malnourished. We will plan a proper nutritional intervention according to our care objectives (symptomatic improvement, cure, exclusively comfort care...) [36]. Cognitive impairments [37, 38] and confusional syndrome are also frequently diagnosed and we can generally provide efficacious treatment for them. Emotional disorders sleep cycle disturbances, and loss of sphincter control will be other geriatric syndromes we can act on. It is also very important to detect situations of caregiver burnout and offer support measures, which will surely impact the quality of life of both our seniors and their caregivers [39].

Avoiding polypharmacy

Inappropriate drug prescription is especially common in older people and is associated with a higher risk of drug-related adverse events, more hospitalizations, and inappropriate resource use [40, 41]. We must also bear in mind the possible interactions between cancer drugs and any other medications the senior may be receiving [42]. We are all aware, for instance, of the interaction between different tyrosine-kinase inhibitors and proton pump inhibitors. Other usual situations are maintaining lipid-lowering treatments in patients with significant weight loss and short life expectancy, or continuing with antihypertensive medication in older individuals with multifactorial anemia that causes hypotension.

Selection of low-toxicity treatment regimes

Systemic treatment of older individuals with cancer poses a challenge for the oncologist, given the variety of situations that must be attended to and the lack of published evidence in most cases. Only in recent years are studies being designed and specific results beginning to appear for this population. EORTC has prioritized this issue [43] and SIOG recommends that trials carried out in older patients evaluate their quality of life, functional status, and independence as priority objectives [44]. On the other hand, certain toxicities in particular, such as the neurotoxicity associated with some cytostatics, should be the object of study on their own [45, 46]. Furthermore, thromboembolic episodes appear to occur more frequently in older individuals who receive bevacizumab [47].

Finally, oral chemotherapy is an appealing option in seniors, due to better compliance in administering it and greater convenience compared to intravenous chemotherapy. Metronomic chemotherapy can represent a means of decreasing toxicity [48–50], thereby enhancing quality of life; moreover, several studies have pointed out the antiangiogenic and immunomodulating effects of this mode of administration [51].

Consequently, our general recommendations for this point would be:

- Insofar as possible, avoid cisplatin and paclitaxel combinations, given their neurotoxicity.
- Avoid anthracyclines in seniors with ejection fractions of less than 50% and consider alternatives, such as liposomal doxorubicin [52].
- Use drugs with a favorable toxicity profile: weekly vinorelbine, gemcitabine, or taxanes.
- Use capecitabine instead of 5-FU infusion.
- Exercise caution with the use of antiangiogenics.
- Avoid concurrent chemo-radiotherapy treatments.
- Consider the benefits of metronomic chemotherapy.

Prevention and early treatment of the toxic effects of chemotherapy

Mucositis [53, 54]. In addition to impacting quality of life in people with cancer, oral mucositis influences treatment decisions and often necessitates dose reductions and delay or even treatment withdrawal. Being older and female are two risk factors for mucositis, for reasons as yet unknown. Deficient nutritional status, smoking, alcohol use, and periodontal disease are other patient-related risks.

Recommendations for mucositis prevention and treatment:

- Early hospitalization in individuals who develop dysphagia and/or diarrhea;
- Nutritional support;
- Oral prophylaxis and hygiene, and
- Attention to new drugs, such as palifermin (keratinocyte growth factors) [55, 56].

Use of granulocytic colony-stimulating factors (G-CSF) and erythropoietin

Historically, when treatment intent was palliative, chemotherapy dose reduction was widespread to decrease the incidence of neutropenia in patients at risk. However, more recent publications maintain that G-CSF use would be justified if treatment intent is to prolong survival, even when it is not curative [57]. The National Cancer Comprehensive Network's recommendations, as well as those of the 2015

American Society of Clinical Oncology (ASCO) [58], both advise primary prevention with G-CSF when the risk of febrile neutropenia surpasses 20%. However, these guidelines also recommend growth factors in people at “special” risk, including those over 65 years of age.

Indeed, already in 2001, SIOG recommended that colony-stimulating factors and erythropoietin be considered a fundamental element of treatment for senior cancer patients who are receiving chemotherapy, whether for radical or palliative purposes [59]. With respect to erythropoietin, it must be remembered that in older individuals, the symptoms that precede the anemia can quickly lead to a decline of their functional dependence.

In short, we believe that the use of colony-stimulating factors should be at least contemplated in all seniors who receive cytotoxic chemotherapy. We must also be especially alert to anemia secondary to chemotherapy and begin early treatment with erythropoietin as per guideline recommendations, particularly in patients with certain comorbidities (cardiac or respiratory), as anemia can have a major clinical and functional impact.

Adequate symptom control

Together with the previously named support and recommendations, it is extremely important to ensure optimal symptomatic control by means of a multidisciplinary approach [60, 61]. The sphere of Palliative Care deals with more issues than simply controlling the individual's symptoms. Treatment aims must be determined to enhance outcomes. Symptom management is similar in older and younger patients, but symptoms in seniors can be associated with complications that are both more common and more serious. In certain neoplasms, such as lung cancer, early palliative treatment associated with cancer-specific treatment has proven to go so far as to influence survival [62].

Our recommendation, therefore, is that any cancer individual that has no possibility for radical oncological treatment undergoes early evaluation by a Palliative Care team, especially if said individual is older, and for this assessment to be on-going throughout the entire process.

Achieve adequate social support [63]

There is little agreement in the literature as to what constitutes adequate social support [64]. Some studies have attempted to quantify social support based on the number of relatives, for instance. Other works examine patients' perception of the quality of their social support [65].

Despite all the difficulties incumbent in defining and quantifying social support, we believe that its necessity is evident and that it must be appraised and optimized for proper treatment planning for seniors with cancer.

Conclusions

Many of the patients who are assessed in routine clinical practice in Oncology are older. CGA is the basic tool by means of which to evaluate older people with cancer and to understand their needs. Training and the correct use of recommendations regarding treatment for comorbidities and geriatric syndromes, support care, and drug–drug interactions and toxicities, including those of antineoplastic agents, as detailed in this article, will ensure that this population is properly managed.

Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The informed consent is not applicable in this paper.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Shih Y-CT, Hurria A. Preparing for an epidemic: cancer care in an aging population. *Am Soc Clin Oncol Educ Book*. 2014;133–7. https://doi.org/10.14694/EdBook_AM.2014.34.133.
- Molina-Garrido M-J, Guillén-Ponce C, Blanco R, et al. Delphi consensus of an expert committee in oncogeriatrics regarding comprehensive geriatric assessment in seniors with cancer in Spain. *J Geriatr Oncol*. 2017;pii: S1879-4068(17)30253-9. <https://doi.org/10.1016/j.jgo.2017.11.012>.
- Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol*. 2005;55:241–52.
- Hurria A. Senior adult oncology, version 2.2014. *J Natl Compr Cancer Netw*. 2014;12:82–126.
- Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Ann Oncol*. 2015;26:288–300.
- Bhuttoo A, Morley JE. The clinical significance of gastrointestinal changes with aging. *Curr Opin Clin Nutr Metab Care*. 2008;11:651–60.
- Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging*. 2006;1:253–60.
- de Kane RL, Ouslander JG, Abrass IB. *Essentials of clinical geriatrics 7/E (Lange Essentials)*. McGraw-Hill Education/Medical.
- Stuck AE, Aronow HU, Steiner A, et al. A trial of annual in-home comprehensive geriatric assessments for elderly people living in the community. *N Engl J Med*. 1995;333:1184–9.
- Stuck AE, Siu AL, Wieland GD, et al. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet (London, England)*. 1993;342:1032–6.
- Terret C, Albrand GDJ. Multidimensional geriatric assessment reveals unknown medical problems in elderly cancer patients. *J Clin Oncol*. 2004;22(14S):81.
- Molina Garrido MJ. Oncogeriatría: una forma de optimizar la atención global del paciente anciano con cáncer. *Nutr Hosp*. 2016;33:177.
- Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol*. 2007;25:1824–31.
- Puts MTE, Hardt J, Monette J, et al. Use of geriatric assessment for older adults in the oncology setting: a systematic review. *J Natl Cancer Inst*. 2012;104:1133–63.
- Pallis AG, Fortpied C, Wedding U, et al. EORTC elderly task force position paper: approach to the older cancer patient. *Eur J Cancer*. 2010;46:1502–13.
- Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32(24):2595–603.
- Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer*. 2005;104:1998–2005.
- Molina-Garrido MJ, Guillén-Ponce C, Castellano CS, et al. Tools for decision-making in older cancer patients. Role of the comprehensive geriatric assessment. *Anticancer Agents Med Chem*. 2014;14(5):651–6.
- Hamaker ME, Seynaeve C, Wymenga ANM, et al. Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: results from the OMEGA study of the Dutch breast cancer trialists' group. *Breast*. 2014;23:81–7.
- Antonio M, Saldaña J, Carmona-Bayonas A. Geriatric assessment predicts survival and competing mortality in elderly patients with early colorectal cancer. Can it help in adjuvant therapy decision-making? *Oncologist*. 2017;22:1–10.
- Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol*. 2012;30:1829–34.
- Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011;29:3457–65.
- Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. *Cancer*. 2012;118:3377–86.
- Hoppe S, Rainfray M, Fonck M, et al. Functional decline in older patients with cancer receiving first-line chemotherapy. *J Clin Oncol*. 2013;31:3877–82.
- Decoster L, Kenis C, Schallier D, et al. Geriatric assessment and functional decline in older patients with lung cancer. *Lung*. 2017;195:619–26.
- van Bekkum ML, van Munster BC, Thunnissen PLM, et al. Current palliative chemotherapy trials in the elderly neglect patient-centred outcome measures. *J Geriatr Oncol*. 2015;6:15–22.

27. Mohile SG, Velarde C, Hurria A, et al. Geriatric assessment-guided care processes for older adults: A Delphi consensus of geriatric oncology experts. *J Natl Compr Cancer Netw*. 2015;13(9):1120–30.
28. O'Donovan A, Mohile SG, Leech M. Expert consensus panel guidelines on geriatric assessment in oncology. *Eur J Cancer Care (Engl)*. 2015;24:574–89.
29. NCCN guidelines Version 1. 2017. Older adult oncology. www.nccn.org. Accessed Jan 2018.
30. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin*. 2016;66:337–50.
31. Grønberg BH, Sundstrøm S, Kaasa S, et al. Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy. *Eur J Cancer*. 2010;46:2225–34.
32. Ngeow J, Leong SS, Gao F, et al. Impact of comorbidities on clinical outcomes in non-small cell lung cancer patients who are elderly and/or have poor performance status. *Crit Rev Oncol Hematol*. 2010;76:53–60.
33. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing*. 2006;35(Suppl 2):ii37–41.
34. Pressoir M, Desné S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer*. 2010;102:966–71.
35. Aaldriks AA, van der Geest LGM, Giltay EJ, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol*. 2013;4:218–26.
36. Bozzetti F. Nutritional aspects of the cancer/aging interface. *J Geriatr Oncol*. 2011;2:177–86.
37. Extermann M. Older patients, cognitive impairment, and cancer: an increasingly frequent triad. *J Natl Compr Cancer Netw*. 2005;3:593–6.
38. Raji MA, Kuo Y-F, Freeman JL, et al. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. *Arch Intern Med*. 2008;168:2033–40.
39. A Guide to Geriatric Syndromes: Common and Often Related Medical Conditions in Older Adults. 2012. <http://www.healthinag.org/resources/resource:guide-to-geriatric-syndromes-part-i>.
40. Keijsers CJPW, van Hensbergen L, Jacobs L, et al. Geriatric pharmacology and pharmacotherapy education for health professionals and students: a systematic review. *Br J Clin Pharmacol*. 2012;74:762–73.
41. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. *Clin Pharmacol Ther*. 2011;89:845–54.
42. Riechelmann RP, Saad ED. A systematic review on drug interactions in oncology. *Cancer Investig*. 2006;24:704–12.
43. Pallis AG, Gridelli C, van Meerbeeck JP, et al. EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population. *Ann Oncol*. 2010;21:692–706.
44. Hurria A, Cohen HJ, Extermann M. Geriatric oncology research in the cooperative groups: a report of a SIOG special meeting. *J Geriatr Oncol*. 2010;1:40–4.
45. Goldberg RM, Tabah-Fisch I, Bleiberg H, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol*. 2006;24:4085–91.
46. McCleary NJ, Dotan E, Browner I. Refining the chemotherapy approach for older patients with colon cancer. *J Clin Oncol* 2014. <https://doi.org/10.1200/jco.2014.55.1960>.
47. Skillings JR, Johnson DH, Miller K, et al. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy. *J Clin Oncol*. 2005;23:3019.
48. Cazzaniga ME, Camerini A, Addeo R, et al. Metronomic oral vinorelbine in advanced breast cancer and non-small-cell lung cancer: current status and future development. *Future Oncol*. 2016;12:373–87.
49. Addeo R, Sgambato A, Cennamo G, et al. Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. *Clin Breast Cancer*. 2010;10:301–6.
50. Camerini A, Puccetti C, Donati S, et al. Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of a phase II trial (MOVE trial). *BMC Cancer*. 2015;15:359.
51. André N, Carré M, Pasquier E. Metronomics: towards personalized chemotherapy? *Nat Rev Clin Oncol*. 2014;11:413–31.
52. Bovelli D, Plataniotis G, Roila F, et al. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2010;21(Suppl 5):v277–82.
53. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. 2007;109:820–31.
54. Bensinger W, Schubert M, Ang K-K, et al. NCCN task force report. Prevention and management of mucositis in cancer care. *J Natl Compr Canc Netw*. 2008;6(Suppl 1):21–4.
55. Ayago Flores D, Ferriols Lisart R. Effectiveness of palifermin in the prevention of oral mucositis in patients with haematological cancers. *Farm Hosp*. 2010;34(4):163–9. <https://doi.org/10.1016/j.farma.2009.12.005>.
56. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004;351:2590–8.
57. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47:8–32.
58. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of clinical oncology clinical practice guideline update. *J Clin Oncol*. 2015;33:3199–212.
59. Repetto L, Biganzoli L, Koehne CH, et al. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer*. 2003;39:2264–72.
60. Balducci L, Dolan D, Hoffer SA. Palliative care in older patients with cancer. *Cancer Control*. 2015;22:480–8.
61. Alexander K, Goldberg J, Korc-Grodzicki B. Palliative care and symptom management in older patients with cancer. *Clin Geriatr Med*. 2016;32:45–62.
62. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733–42.
63. Kroenke CH, Kwan ML, Neugut AI, et al. Social networks, social support mechanisms, and quality of life after breast cancer diagnosis. *Breast Cancer Res Treat*. 2013;139:515–27.
64. Gallant MP. The influence of social support on chronic illness self-management: a review and directions for research. *Health Educ Behav*. 2003;30:170–95.
65. Shor E, Roefls D, Yogeu T. The strength of family ties: a meta-analysis and meta-regression of self-reported social support and mortality. *Soc Netw*. 2013;35:626–38.